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Enterohepatic circulation and cholestasis

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SUMMARY

Sulfated glycolithocholic acid, a major metabolite of the secondary bile acid lithocholic acid in newborns, is highly cholestatic when administered to experimental animals. Its taurine conjugated analogue, on the other hand, is less hepatotoxic. This thesis deals with the pathophysiology of the potentially toxic lithocholic acid sulfates and the possibilities of dietary intervention to prevent their toxic effects.

It was found that elevated serum levels of sulfated lithocholic acid conjugates in children develop during the course of cholestatic liver disease, due to the well documented shift of bile acids from the enterohepatic to the systemic circulation and/or their increased formation in the liver during cholestasis. However, elevated serum levels may also be the result of an increased influx of these compounds from the intestine, as appeared from reproducible postprandial elevations in serum concentration of the sulfated bile acids after a standardized testmeal in a specific group of patients, which could be prevented by addition of cholestyramine to the testmeal (Appendix paper 1).

Animal studies aimed at the characterization of the enterohepatic circulation of sulfated lithocholic acid conjugates have been performed in unanesthetized and unrestrained rats with normal feeding behaviour, in which the enterohepatic circulation could be interrupted and restored without direct surgical intervention (Appendix paper 2). The use of pentobarbital- anesthesia significantly affected the process of bile formation as well as intestinal bile acid absorption in the rat (Appendix paper 3).

Sulfated lithocholic acid conjugates were efficiently absorbed from the intestine when administered at physiological infusion rates. Absorption was not appreciably inhibited by excess of unsulfated bile acids. However, the presence of excess of calcium in the intestinal lumen selectively reduced their absorption (Appendix paper 4). Sulfated lithocholic acid conjugates were secreted into bile without further hepatic metabolism; urinary secre-

tion was negligible under non-cholestatic conditions. The mechanism of their biliary secretion, studied in rats with an undefined genetic defect in biliary secretion of organic anions, was shown to be different from that of unsulfated bile acids, and probably identical to that of organic anions as bilirubin and dibromosulphthalein (Appendix paper 5).

Low doses of enterally administered sulfated glycolithocholic acid caused a reduction of the biliary secretion of phospholipids and cholesterol, without affecting bile acid secretion and bile flow. This may have been due to interference of the sulfated compound with intracellular lipid transport to the bile canaliculi, or to effects at canalicular level, e.g. by disturbing micellar aggregation. This reduction of biliary lipid secretion may be an initiating event in sulfated glycolithocholic acid-induced cholestasis (Appendix paper 6). Cholestasis was readily induced by intravenous administration of relatively small amounts of sulfated glycolithocholic acid in rats with a depleted endogenous bile acid pool. The presence of endogenous bile acids prevented this cholestatic action, by 1) acceleration of the biliary elimination of the toxic compound, and 2) the maintenance of a high bile flow, which prevented precipitation of the compound in bile canaliculi and/or ductuli (Appendix paper 7). The differences in the hepatotoxic properties between sulfated glyco- and tauro lithocholic acids may, at least partly, originate from their differential interactions with calcium; the former rapidly precipitated with calcium in a 1:1 stoichiometry *in vitro*, whereas the latter did not. Formation of calcium- sulfated glycolithocholic acid complexes may be an important factor in the development of cholestasis *in vivo* (Appendix paper 8).

Protection of the liver from sulfated lithocholic acid- induced hepatotoxicity can theoretically be exerted at hepatic level by: 1) increasing the availability of taurine for conjugation by dietary means. However, pharmacological doses of taurine are required to alter the pattern of bile acid conjugation significantly in man. 2) maintenance of a high bile flow to accelerate the biliary excretion of the

toxic compounds and to prevent their precipitation in the hepatobiliary system. Protection *in vivo* is probably mainly mediated at intestinal level, by withdrawal of the cholestatic sulfated bile acids from the ente-

rohepatic circulation. Binding of sulfated lithocholic acid conjugates to insoluble calcium phosphate in the intestinal lumen (Appendix paper 8) may be of physiological importance in this respect.

INTRODUCTION

The formation of bile is a function of the liver. Bile is a solution, containing organic electrolytes and trace elements, phospholipids, cholesterol and the main organic constituents for the maintenance of normal bile flow. Bile is essential for the elimination of a number of endogenous and certain xenobiotics, in many cases after transformation in the liver. Bile is required for the intestinal absorption of lipid soluble vitamins and an essential role in bile acids. Bile acids are major determinants of bile flow: a close correlation exists between bile flow and hepatic bile acid secretion. Second, by their ability to solubilize bile acids maintain water-soluble constituents such as cholesterol, fatty acids and monoglycerides in solution (3). A significant role in the solubilization of the products of fatty acid and monoglyceride metabolism in the bile. Their intestinal absorption is conserved in an efficient manner, allowing a high concentration in order to maintain concentrations at the site of action.

Cholestasis refers to a condition in which bile flow is decreased or stopped. It is well established that bile flow is altered during cholestasis. There will be a shift of bile acids from the enterohepatic to the systemic circulation, an altered hepatic secretion of bile acids, and in the formation of detergent metabolites, and primary bile acid excretion. Whether bile acids contribute to the pathogenesis of human cholestasis